Placebo:

P42868ELF Basal cell cancer nose, T1N0M0 6/20/94
P58494ARZ Squamous cell carcinoma in situ of the arm 10/9/92
P16563THM Basal cell cancer 1/24/94
P47311TOM Skin cancer, NOS 5/4/95
P58494ARZ SCCA in situ of forearm 10/9/92; placebo
P38166JSM 10/5/94 Oral lichen planus
P47522CIN 7/9/96 SCCA leg

Tamoxifen:

P27665SYR Basal cell carcinoma, 7/8/94
P30220PGH Well-differentiated SCCA arm, 9/14/93
P28162BCC Basal cell carcinoma, 5/96 and 7/7/96

During a meeting with the sponsor, the NSABP stated that skin cancers were excluded from their analyses. These cancers are not immediately life-threatening. The reviewer agrees with the sponsor's decision to exclude these cancers from the analysis.

2. Two cancers were recorded in the CRF but not in the database:

P52275JSM Polycythemia vera 11/9/94. Randomized to tamoxifen.
P29571BSF Myelodysplastic syndrome 4/10/97. Randomized to placebo

The NSABP indicated 9/23/98 that they routinely did not include these diseases in counts of invasive cancers. They will do so in the future.

3. Information on non-invasive endometrial cancer was collected, but data on non-invasive cervical cancer was not.

4. Overall, there is no difference in the occurrence of cancers other than breast and endometrium between treatment arms. Fornander and colleagues reported an excess risk of GI cancers associated with tamoxifen; no excess risk is seen in this large prospective randomized trial. Some investigators have reported an excess risk of ovarian cancer with tamoxifen administration; no such excess risk was observed in this study.

10.4 Cardiovascular events

A variety of cardiovascular events occurred on the trial and were summarized by the sponsor in the ERSMAC report:

Table 46. Cardiac and vascular events among BCPT participants (Table 14, ERSMAC report, volume 3, page 25

Types of events	Placebo	Tamoxifen	Total
Ischemic heart disease:	59	61	120
Fatal MI	8	7	15
Non-fatal MI	19	20	39
Angina w/ PTCA or CABG	12	12	24
Acute ischemic syndrome*	20	22	42
Other CV death	4	5	9
Other vascular:	80	111	191
Fatal stroke	3	4	7
Non-fatal stroke	21	30	51
TIA	21	18	39
Fatal PE	0	2	2
Non-fatal PE	6	15	21
Deep vein thrombosis w/o hospitalization	3	3	6
Deep vein thrombosis w/ hospitalization	16	27	43
Peripheral vascular disease	10	12	22
TOTAL	143	177	320

*New Q-wave on ECG but no angina or elevation of serum enzymes; or angina requiring hospitalization without PTCA or CABG

The reviewer discusses these events separately, categorized as cardiovascular events (MI, angina, acute ischemic syndrome, other CV death), stroke/TIA, peripheral vascular disease, and thromboembolic events (DVT, PE).

10.4.1 Ischemic heart disease

Ischemic heart disease was defined, in descending order of severity, as fatal myocardial infarction, non-fatal myocardial infarction, angina requiring angioplasty or coronary artery bypass graft, or acute ischemic syndrome. Participants who experienced more than one of these events were assigned to the worst category.

In the NSABP P-1 manuscript, a table of the annual hazard rates for ischemic heart disease was presented:

Table 47. Average annual hazard rates of ischemic heart disease (Table 6, submitted manuscript, P-1)

Event	Number of events		Rate/1000 women		Risk ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
MI:	27	27	1.13	1.13	1.00	0.57-1.78
Fatal	8	7	0.33	0.29	0.88	0.27-2.77
Non-fatal	19	20	0.79	0.84	1.06	0.54-2.09
Angina*	12	12	0.50	0.50	1.00	0.41-2.44
Acute ischemic syndrome#	20	22	0.84	0.92	1.11	0.58-2.13
TOTAL	59	61	2.47	2.57	1.04	0.71-1.51

*Requiring angioplasty or CABG
#New Q-wave on ECG; no angina or elevation of serum enzymes; no angina requiring hospitalization without surgery

There was no difference between treatment arms for any of these parameters.

Reviewer Comment:

1. Some of the events reported in Table 47 occurred after participants had discontinued study drug. These events are summarized below.

Table 48. Ischemic cardiac events that occurred after study drug was discontinued

Event	Placebo	Tamoxifen	Total
MI	6	4	10
Severe angina	4	3	7
Acute ischemic syndrome	4	3	7

The events occurred 1 month to 4 years after stopping study drug. If one excludes the events that occurred off study, the conclusions of the NSABP are not altered. Given that tamoxifen may have long-term effects on the incidence of cardiovascular disease, the reviewer agrees that all events that occurred in participants should be reported.

2. When the study was designed, the statisticians discussed the likelihood that participants would be at lower risk for cardiovascular disease than the general population. The risk factors for cardiovascular disease in the study population were examined using the electronic database tables submitted 7/31/98.

Risk factors in the entire study population:

a. Reported past cardiovascular events and baseline cardiac medications

A query of the database for pre-existing cardiovascular disease (past history of angina, heart attack, heart failure, heart murmur, transient ischemic attack, stroke, or

vascular problems) demonstrated that 1648 participants on placebo (25% of the treatment arm) and 1555 of participants on tamoxifen (23%) had a past history of one or more of the above events. Four hundred seventy-eight women on placebo (7%) and 949 on tamoxifen (14%) reported prior or current used of heart medications (exclusive of aspirin and antihypertensive therapy). These numbers are not balanced, but reflect a small part of the study population and probably had little impact on study results. Overall, few participants had had prior ischemic cardiac events, and few women required drug treatment of non-hypertensive cardiovascular problems.

b. Risk factors for ischemic heart disease

Risk factors for ischemic heart disease include a family history of cardiac events at a young age, tobacco use, hypercholesterolemia, diabetes mellitus, and hypertension. The distribution of these parameters is summarized in the following table:

Table 49. Cardiac risk factors among BCPT participants

RISK FACTORS	PLACEBO		TAMOXIFEN	
	Number	Percent	Number	Percent
Diabetes:				
No	6443	96%	6402	96%
Yes	264	4%	279	4%
Hypertension:				
No	5219	78%	5204	78%
Yes	1488	22%	1477	22%
Use of cholesterol-lowering drugs:				
No	6152	92%	6143	92%
Yes	555	8%	538	8%
Family history of MI*:				
No	3552	53%	3611	54%
Yes	3155	47%	3070	46%
Ever smoked:				
No	3499	52%	3378	51%
Yes	3208	48%	3303	49%
Current smoker:				
No	5867	87%	5821	87%
Yes	840	13%	860	13%
Amount smoked:				
≤ 1 ppd	611	73%#	665	77%#
1-2 ppd	212	25%#	173	20%#
2-3 ppd	16	2%#	21	2%#
3-4 ppd	1	0.1%#	1	0.1%#

*First-degree relatives only
Of current smokers

Twenty-two percent of participants on each arm had a baseline diagnosis of hypertension. Four percent of the population on each arm had a diagnosis of diabetes mellitus, and 8% required medication to lower their cholesterol. While half the women in the trial had smoked in the past, only 13% were current smokers. The amount smoked per day was balanced between treatment arms.

When history of diabetes, hypertension, cholesterol-lowering agents, current tobacco use, and MI in a first degree relative were combined, 4360 (65%) of the women on placebo and 4294 of women on tamoxifen (64%) had at least one risk factor for a cardiovascular event. This high percentage may be misleading, as family history of MI in a first-degree relative is probably the contributing factor to the total. No information was obtained about the first-degree relative's age at MI; the family history is significant only in young first-degree relatives (less than age 50 or 55). If one excludes family history

from the risk assessment, 38% of the population and on each study arm had a cardiac risk factor.

3. Risk factors in participants with ischemic heart disease events:

a. History of prior events

Table 50. Ischemic heart events prior to study entry in participants with cardiac events on study

Prior event	Placebo	Tamoxifen	Total
Hx angina	14	17	31
Hx MI	7	9	16
Hx CHF	3	1	4
Hx heart murmur	5	4	9
Hx hypertension	31	35	66
Hx diabetes mellitus	12	17	29
Hx TIA	3	2	5
Hx CVA	0	2	2
Hx vascular problems	7	7	14

Ninety-one of the 120 participants with a cardiac event had a prior history of one of the above events (75%).

b. History of risk factors

The electronic database was queried regarding baseline risk factors in women with myocardial infarction, angina, acute ischemic syndrome, and other cardiovascular death. These queries are not shown, but 75-85% of women with these syndromes had existing risk factors for cardiovascular disease at entry.

c. Overall, a high proportion of women with a cardiac event had a history of prior cardiac events or cardiac risk factors. The factors were balanced between treatment arms.

4. Another category of "other vascular death" was listed by the sponsor. Deaths in nine participants, 4 on placebo and 5 on tamoxifen, were included. These deaths consisted of complications from cardiomyopathy and sudden death.

5. The cardiac events of MI, angina, acute ischemic syndrome, and other cardiovascular death were analyzed by age at randomization:

Table 51. BCPT Cardiac events by age

Age	Placebo	Tamoxifen	Total
≤ 49	5	9	14
50-59	15	15	30
≥ 60	43	42	85
Total	63	66	129

While there appear to be more events in women under age 50 on tamoxifen compared to placebo, there are few events in this age category and the difference is not significantly different (p-value 0.60 for the overall distribution; p-value 0.40 for women ≤ 49 specifically). There is no significant difference between treatment arms for women aged 50 or more, or within the prospectively defined age groups of 50-59 and 60+. Younger women, as expected, had fewer events than older women.

6. These data do not support a cardioprotective effect of tamoxifen. However, the statistical section of the protocol noted that the statistical power to detect a benefit of tamoxifen would depend on the age of the participants. Ten thousand postmenopausal women were mentioned as the target accrual to demonstrate this benefit; fewer than this target goal were accrued. While this trial does not demonstrate a cardiovascular benefit from tamoxifen, the trial may be underpowered to show a difference.

7. Considering the risk factors present in the overall study population, it was not possible to predict who would develop future cardiac events.

10.4.2 Stroke and transient ischemic attacks

Women who experienced both a TIA and a stroke were categorized as the more severe event, i.e. CVA. The number of strokes was increased on the tamoxifen arm, although not significantly so:

Table 52. Stroke and TIA on NSABP P-1

Event	Placebo	Tamoxifen	Total
Fatal stroke	3	4	7
Non-fatal stroke	21	30	51
TIA	21	18	39
Total	45	52	97

In the NSABP P-1 manuscript, the authors presented the annual hazard rate for these events in the total population and by age:

Table 53. Average annual hazard rates of vascular-related events by age at entry (NSABP P-1 manuscript, Table 8).

Event	Number of Events		Rate/1000 Women		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Stroke	24*	34#	1.00	1.43	1.42	0.82-2.51
≤ 49	4	3	0.42	0.32	0.76	0.11-4.49
≥ 50	20	31	1.38	2.13	1.55	0.86-2.87
TIA:	21	18	0.88	0.75	0.86	0.43-1.70
≤ 49	4	3	0.43	0.32	0.76	0.11-4.49
≥ 50	17	15	1.17	1.03	0.88	0.41-1.88

*3 fatal
#4 fatal

Six of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the tamoxifen group were categorized as hemorrhagic. Seventeen of the 34 strokes on the tamoxifen arm were considered occlusive and 7 were considered to be of unknown etiology. Fourteen of the 24 strokes on the placebo arm were reported as occlusive and 4 of unknown etiology.

The authors concluded that there was no difference in the incidence of TIAs between the 2 treatment arms, either for the entire population or by age. The number of strokes was increased, although not significantly so, in women over age 50.

Reviewer Comment:

1. Case report forms for stroke were reviewed by Donna Griebel, M.D., who wrote the following analysis .

2. Fatal stroke:

An Access Query of the database yielded 7 participants whose deaths were attributed to CVA. The death of one participant on that list, **P16874 UCL** (Tamoxifen), was attributed to CVA on the death certificate, but the reviewers believe her death was due to pancreatic cancer. Participant **P56876 MSU** (Tamoxifen) was not included in the Access Query list, and the reviewers believe that her death was due to CVA and not to metastatic lung cancer. These cases were discussed in section 10.1, Deaths. These changes do not change the total number of fatal strokes reported on each arm.

3. Hemorrhagic stroke:

The reviewer's totals of hemorrhagic events on each arm differed slightly, based on review of the case report forms. The reviewer noted 11 events on the tamoxifen arm that could be attributed to intracranial hemorrhage. The additional participant on the reviewer list **may** be **P31396 HAW** who was found to have evidence "thought to represent subacute subarrachnoid hemorrhage" on MRI and MRA performed for work-up of new onset headaches. The abnormal areas were noted in the right subfrontal cistern, two segments of interhemispheric cistern, and right middle cerebral artery cistern.

The reviewer noted 7 events in the placebo group that could be considered hemorrhagic. The additional event on the reviewer's list **may** be **P14725 NSU**. This participant had two events on study, but was only counted as one event. The first, 6/23/95, was an MRI read as probable petechial hemorrhage in the right posterior parietal region and 5 mm lacunar infarct in the left thalamus. The exam was ordered to investigate abnormal findings on a bone scan performed for multiple joint pain. The participant was otherwise asymptomatic at the time. The second event on 1/9/96 was a right corona radiata infarct without evidence of hemorrhage. The participant presented with new onset left sided weakness, facial droop, and slurred speech during an admission for malignant hypertension.

Of note, two of the hemorrhagic strokes on the tamoxifen arm were post-traumatic subdural hematomas. One of the hemorrhagic strokes on the placebo arm was a subdural hematoma, subacute to chronic, with no history given of trauma.

4. Occlusive stroke:

It is unclear what criteria were used to designate a stroke occlusive vs. of unknown origin in the study, and the reviewer's tabulation of each subtype does not match that in the study report. In addition, there were participants with multiple events that were only counted as a single stroke. **P14725 NSU** (Placebo) was considered by the reviewer as having had two CNS events – one hemorrhagic as noted above. **P13809 SIO** (Tamoxifen) was considered to have had at least two CNS events. **P17878 MID** (Tamoxifen) had two events – one occurred approximately 5 months after stopping study medication.

5. Risk factors for occlusive stroke

The majority of participants on each arm of the study who had CNS events (stroke) considered non-hemorrhagic were found by the reviewer to have had at least one risk factor for occlusive stroke, based on medical history data available in the case report forms in the form of self report, medical records from hospitalizations, or deduced from medication lists. Two participants on the placebo arm and 5 participants on the tamoxifen arm had no discernible risk factor other than age. The placebo participants without other risk factors were 63 and 60 years of age. Those on the tamoxifen arm were 76, 75, 69, 60, and 50 years of age. Risk factors noted included hypertension, diabetes, hyperlipidemia, atrial fibrillation/flutter, tobacco use, coagulopathy, prior history of TIA, symptomatic coronary artery disease, and documented significant carotid atheromatous plaques. Eleven of the tamoxifen and 4 of the placebo group had only one discernible risk factor beyond age. Nine of the tamoxifen and 4 of the placebo group had 2 risk factors. Four in each group had 3 risk factors, and 2 in the tamoxifen group had 4 risk factors.

When the documented hemorrhagic CNS events were excluded, the reviewer found 23 participants with 25 events on the tamoxifen arm, and 18 participants with 18 events on the placebo arm who had not had documented hemorrhagic events. One of the tamoxifen participants (P16874 UCL) had had no imaging performed and, conceivably, could have had a hemorrhagic event. She had metastatic pancreatic carcinoma and died

before imaging studies could be performed to diagnose the etiology of her neurologic symptoms.

If it is assumed that the tamoxifen participant without radiographic documentation did not have a hemorrhagic event, the relative risk of an occlusive/ischemic CNS event on tamoxifen/placebo = 1.39, slightly less than the overall relative risk for all types of CNS events reported for the study. If she is not counted, the relative risk is lower still - 1.33.

Treatment with tamoxifen has previously been reported to be associated with increased risk for arterial thrombotic events. Saphner, et al (*Journal of Clinical Oncology, vol. 9, No 2, 1991: pp. 286-294*) reported in their review of the records of 2673 patients who had participated in seven ECOG studies of adjuvant breast cancer therapy, that premenopausal patients treated with a combination of adjuvant chemotherapy and tamoxifen had a significantly higher incidence of arterial thrombosis than those who were treated with chemotherapy alone (1.6% vs. 0.0%, p=0.004). Postmenopausal patients in these studies, however, did not demonstrate a significantly increased risk with the addition of tamoxifen to adjuvant chemotherapy. The incidence of arterial thrombosis in postmenopausal patients on adjuvant chemotherapy combined with tamoxifen was 1.0% compared to 1.7% in an observation group, (p=0.31). The incidence of arterial thrombosis in postmenopausal patients on tamoxifen alone in this study was 1.2%. The arterial thrombotic events that did occur associated with tamoxifen in this analysis were observed while on therapy, not after stopping therapy, and they tended to occur during early cycles of therapy. The time to both venous and arterial thrombotic events with tamoxifen in this analysis was found to be 1-11 months. Of 22 total arterial events, only 10 were cerebral vascular accidents. Eleven were embolic events involving an extremity and one was a mesenteric artery thrombosis.

6. Time to event

In light of this prior analysis, the reviewer examined the non-hemorrhagic strokes reported in this study from the standpoint of whether the event occurred while on active treatment with study drug, and, if that was so, whether the event occurred early during the course of treatment. For this exploratory analysis the reviewer selected the time frame of $\leq$ 1 year from start of therapy as the definition of "early". This time was based on the cited reference, which found the majority of vascular events associated with tamoxifen as having occurred $\leq$ 11 months on treatment.

Eighteen events in 17 participants occurred before stopping tamoxifen treatment on study. Thus 72% of the events (in 74% of the patients with these events) on the tamoxifen arm occurred while on active treatment. Conversely, 28% of the events (in 26% of the patients with such events) on the tamoxifen arm occurred after having stopped treatment. Six of the seven post-treatment events occurred less than 12 months after stopping tamoxifen, and one occurred at 2 years. The tamoxifen post-treatment events are summarized in the table below.

Table 54. Non-hemorrhagic Events Which Occurred **After** End of Therapy – Tamoxifen Arm

Participant	**Time After Stop**	**Time on Treatment**	**Age at Study Entry**	**Approximate Age at Event**
P31095 RCH	25	27	69	73
**P16874 UCL – undocumented (pancreatic ca)	6	12	66	67
P56876 MSU	4	27	60	62
*P25300 BOS	11	24	57	59
*P32029 NVM	10	4	56	57
P31828 DEL	2	60	50	55
P17878 MID (undocumented, second event)	5	43	50	54

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

** = *No radiographic imaging performed to determine the etiology*

The median time to event after stopping tamoxifen was 6 months. The median duration of therapy prior to event for these participants was 27 months. One of the participants, **P16874 UCL**, had metastatic pancreatic cancer and no imaging performed to confirm CVA as opposed to brain metastasis as the etiology of her symptoms before her death. When this participant was excluded, the median time to CNS event after stopping tamoxifen increased slightly to 7.5 months, but the median duration of therapy before event did not change. On the placebo arm 17 events in 17 participants occurred before stopping treatment on study. Only one participant had a non-hemorrhagic CNS event after stopping therapy, and that occurred 1 year after stopping treatment. That participant is summarized in tabular form below.

Table 55. Non-hemorrhagic Event Which Occurred **After** End of Therapy– Placebo

Participant	**Time After Stop (months)**	**Time on Treatment (months)**	**Age at Study Entry**	**Approximate Age at Event**
*P26783 MAR	12	22	63	65

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

Tables 56 and 57 summarize events that occurred on study treatment. Seven of the 18 events that occurred before stopping treatment on the tamoxifen arm were observed at ≤ 12 months after starting therapy, 39%. Three of the 17 such events on the placebo arm occurred ≤ 12 months after starting therapy, 18%. The median time to first

event occurring prior to discontinuing treatment on the tamoxifen arm was 15 months. The median time to first such event on the placebo arm was longer, 34 months. The median age at study entry of those participants who experienced a non-hemorrhagic stroke before stopping therapy on the tamoxifen arm was 69 years (71 yo at time of event), and 68 years on the placebo arm (71 yo at time of event). Nine of the 17 participants on the tamoxifen arm had treatment on study stopped related to the CNS event (53%), while 7/17 participants (41%) on the placebo arm had treatment on study stopped because of the event.

Table 56. Non-Hemorrhagic Events Which Occurred *Before* End of Therapy - Tamoxifen

Participant	TIME (months)	Age at Study Entry	Approximate Age at Event	Off Therapy for Event	Menopausal Status
P40745 HAW	40	67	70	Yes	Post
P23354 PGH	48	75	79	Yes	Unknown
P21802 TOM	39	73	76		Post
*P49920 SML	9	59	59		Post
*P17266 NVM	2	69	69	Yes	Post
P13809 SIO	12 *31	72	73 74		Post
P46726 WIS	48	75	79		Post
P43366 MAR	15	52	53	Yes	Unknown
P39539 HAW	43	76	79		Unknown
*P34465 ARZ	54	75	79		Post
P21927 DUL	9	68	68		Post
*P45572 DAN	10	56	56		Post
P18676 NVM	2	68	68	Yes	Unknown
P30144 KEN	12	63	64	Yes	Post
P48542 MDA	15	76	77	Yes	Post
P12855 SCR	56	57	61	? 2 months after event for toxicity?	Post
P17878 MID	43	50	53	Yes	Pre

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

Table 57. Non-hemorrhagic Events Which Occurred *Before* End of Therapy - Placebo

Participant	Time (Months)	Age at Study Entry	Approximate Age at Event	Off Therapy for Event	Menopausal Status
P07360 BAY	34	66	69	Yes	Unknown
P20088 SML	58	74	78		Unknown
*P28618 STA	42	68	71	Yes	Post
P04962 NVM	14	54	55	Death from CVA	Post
P39467 UPA	7	60	60	Yes	Unknown
P14725 NSU	21	71	72		Post
P24383 CIL	29	72	74		Unknown
P28611 BOS	51	69	73	Yes	Post
P29571 BSF	42	77	80		Post
P45196 JSM	33	50	52		Unknown
*P17986 NVM	41	51	54		Unknown
P01130 HOG	36	77	80		Unknown
*P55450 MON	3	63	63		Post
*P44243 MON	46	72	75		Post
P25278 HOP	38	47	50		Unknown
P24838 OCH	22	73	74	Yes	Unknown
P14031 CAR	6	47	47	Yes	Pre

* = *CT findings normal or with evidence of multiple old lacunar infarcts concurrent with clinical findings consistent with a lacunar infarct. No evidence of hemorrhage*

In this exploratory analysis, the median time to non-hemorrhagic stroke while on active treatment was shorter on the tamoxifen arm, and a higher percentage occurred within the first year of treatment. More events were noted after stopping study treatment on the tamoxifen arm.

The paper by Saphner, et al, noted the risk for arterial thrombotic events to be significantly increased in the premenopausal adjuvant population and not the postmenopausal population represented in the studies analyzed. In contrast, the majority of participants (12/17) on the tamoxifen arm in this prevention trial that had a non-hemorrhagic CNS event before end of therapy were postmenopausal - either reporting a date of menopause or date of bilateral oophorectomy. Only 1/17 reported premenopausal status at study entry. The remaining four gave a history of a total abdominal hysterectomy, but there was no definite menopausal status provided in the data set. The ages of these four patients – 75, 76, 68, and 52 – indicate that three were likely to have been postmenopausal. Of the participants on the placebo arm with a non-hemorrhagic stroke prior to stopping therapy, 7/17 reported a date of menopause or bilateral oophorectomy. Only one reported a premenopausal status, and the remaining 9 were of uncertain menopausal status, although four were ≤ 60 years of age – 50, 51, 47, and 60 yo. The authors of the referenced paper, however, expressed reservations regarding

drawing the conclusion that tamoxifen does not influence the incidence of arterial thrombotic events in the postmenopausal population, as the results of the analysis could have been influenced by the data from one of the studies included, EST 1178 (169 patients randomized between adjuvant treatment with tamoxifen or placebo). The incidence of arterial thrombotic events on the placebo arm in that study was much higher than expected, 4.8%. The incidence was higher not only than that observed on its tamoxifen arm (1.2%), but on all arms of the other studies examined in that analysis. The reason for the skewed incidence in the placebo arm of EST 1178 is unknown.

7. In conclusion, the reviewer confirmed a slightly higher risk of arterial thrombotic events on the tamoxifen arm compared to placebo in this prevention trial. Exploratory analyses suggested a trend for earlier thrombotic events on the tamoxifen arm when compared to the placebo arm as well. The overwhelming majority of patients with such events were postmenopausal and had significant underlying risk factors for developing thrombotic strokes. Most events occurred while on active treatment – on both the tamoxifen and placebo arms – but there were more post-treatment events in the tamoxifen group than the placebo group. Previous reports, however, have correlated arterial thrombotic events associated with tamoxifen with the active treatment phase, and not after treatment cessation.

10.4.3 Thromboembolic Events

The following thromboembolic events were reported by the NSABP:

Table 58. Thromboembolic events in NSABP P-1

Type of events	Placebo	Tamoxifen	Total
Fatal PE	0	2	2
Non-fatal PE	6	15	21
Deep vein thrombosis w/o hospitalization	3	3	6
Deep vein thrombosis w/hospitalization	16	27	43

The NSABP reported 49 women with DVT on the trial, 19 on placebo compared with 30 on tamoxifen. The investigators distinguished events requiring hospitalization from those managed as an outpatient. However, only 3 women on each arm were not hospitalized for the event; most were admitted.

Seventeen women in the trial were originally reported with a pulmonary embolus, 6 on placebo and 17 on tamoxifen. Originally, 2 of these events, both on the tamoxifen arm, were reported as fatal (see reviewer comment below).

Thirty women on tamoxifen were diagnosed with DVT compared to 19 women on placebo.

The following hazard ratios for these events were reported in the NSABP P-1 manuscript:

Table 59. Average annual hazard rates of vascular-related events by age at entry (from Table 8, NSABP P-1 manuscript)

Event	Number of Events		Rate/1000 Women		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
PE:	6	18*	0.25	0.75	3.01	1.15-9.27
≤ 49	1	2	0.11	0.21	2.02	0.18-22.32
≥ 50	5	16	0.34	1.10	3.20	1.12-11.17
DVT**:	19	30	0.79	1.26	1.59	0.86-2.98
≤ 49	8	10	0.85	1.08	1.27	0.45-3.69
≥ 50	11	20	0.76	1.38	1.82	0.83-4.20

*3 fatal

**All but 3 cases in each arm required hospitalization

The sponsor concluded that there were an excess number of events on the tamoxifen arm, concentrated in women age 50 or more.

Reviewer Comments: Deep vein thrombosis

1. In the grading of DVT severity, grade 1 was defined as thrombophlebitis, grade 2 as DVT not requiring hospitalization, grade 3 as DVT requiring hospitalization, and grade 4 as pulmonary embolism. The revised CTC criteria for thrombosis/embolism are as follows:

Event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Thrombosis/ embolism	None	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism

These criteria were recently published and were not available when the study was designed. They are more in keeping with clinical practice, as they distinguish between events which do and do not require therapeutic intervention. The distinction between grade 2 and grade 3 events, as defined in the trial, is not clinically meaningful. Therefore, the total number of deep vein thromboses should be considered in the risk-benefit assessment of the trial.

2. An additional case was identified during review of case report forms. P47463EIN was randomized to tamoxifen 9/8/92; the risk assessment forms were not present in her CRF. She was diagnosed with cancer of unknown primary at age 62 on 4/12/96. She discontinued study drug 4/23/94 due to the adverse publicity about the P-1 trial. A CT scan 4/17/96 demonstrated subclavian vein thrombosis.

In the reviewer's opinion, although the participant was randomized to tamoxifen, it is unlikely that this event is related to study drug given the timing of its occurrence.

3. Some of the DVTs listed in Tables 58 and 59 occurred after study drug was discontinued:

Table 60. DVTs that occurred after study drug was discontinued:

	Placebo	Tamoxifen	Total
DVT	10	3	13

The ten events on the placebo arm occurred from 2 months to 3 years after stopping study drug. On tamoxifen, the 3 events that occurred after study drug occurred within 19 to 33 days of discontinuing study drug, at a time when tamoxifen blood levels are still detectable. If one excludes events on placebo that occurred after study drug was stopped, the comparison is between 9 DVTs on placebo and 30 on tamoxifen, a more striking difference.

4. The CRFs of the participants who experienced DVT were reviewed. Predisposing factors are summarized as follows:

Table 61. Predisposing factors in women with DVT

Factor	Placebo (n=19)	Tamoxifen (n=30)	Total (n=49)
Weight:			
<155 lbs	3 (16%)	6 (20%)	9 (18%)
156-175 lbs	5 (26%)	7 (23%)	12 (24%)
> 175 lbs	11 (58%)	17 (57%)	28 (57%)
Tobacco:			
Past/current tob	11 (58%)	13 (43%)	24 (49%)
Current tobacco	5 (26%)	3 (10%)	8 (16%)
Precipitating event:			
Surgery/general anesthesia	6 (32%)	10 (33%)	16 (33%)
Long trips	2 (11%)	2 (7%)	4 (8%)
Trauma	2 (11%)	1 (3%)	3 (6%)
Underlying predisposing medical disorder:			
Malignancy	5* (26%)	1 (3%)	6 (12%)
Subclavian catheter	1 (5%)	0	1 (3%)
Thoracic outlet syndrome	1 (5%)	0	1 (3%)
Open-label tamoxifen	1 (5%)	0	1 (3%)
Protein S/protein C deficiency	1 (5%)	1 (3%)	1 (3%)
Enlarged uterus	0	1 (3%)	1 (3%)

*Includes 2 breast cancer patients who are also listed under "open-label tamoxifen" and "subclavian catheter" and 1 glioma patient included under "surgery"

Approximately 80% of the women in each group were above the population median for weight; 58% of women on each arm weighed over 175 pounds. Fifty-eight percent of women with DVT on placebo had a past or current history of smoking compared to 43% of women with DVT on tamoxifen; fewer women on tamoxifen with a DVT had a current smoking history.

Predisposing events or medical conditions are discussed by arm.

Placebo:

Ten of the 19 women on placebo had a predisposing event, such as surgery, trauma, or a long trip prior to the development of clot. Six participants had medical conditions that increased the likelihood of clotting. These conditions are detailed below:

- A participant on the placebo arm was diagnosed with invasive breast cancer. Her therapy was unblinded and she was placed on open-label tamoxifen. Her deep vein

thrombosis occurred while on tamoxifen. She is included on the placebo arm in an intent-to-treat analysis, but had a tamoxifen-related event.

- Two women experienced subclavian vein thromboses, included in the count of DVT. One woman had documented pressure from the first rib, requiring a rib resection. The second developed a clot in her indwelling catheter while receiving chemotherapy for invasive breast cancer.
- Two participants were diagnosed with cancer without other events (pancreatic cancer with liver metastases diagnosed 2 months prior to the DVT; 1 woman diagnosed with T2N0M0 invasive breast cancer approximately 1 year prior to the DVT with no antineoplastic therapy documented in the CRF).
- One participant experienced 3 separate clotting events and was found to have protein S and protein C deficiency.

Overall, 16 of the 19 participants on placebo who experienced a DVT (84% of this group) had an associated event known to increase clotting risk.

Tamoxifen:

On the tamoxifen arm, 17 of the 30 participants with a DVT (57%) had a predisposing event, including surgery with general anesthesia, prolonged immobility associated with travel, and trauma. Other medical events included:

- Two women had a diagnosis of malignancy
- One woman was described in the CRF as having protein C deficiency, although protein C levels were measured while anticoagulated. It is unlikely that she has a true deficiency.
- One woman had a pelvic ultrasound performed at the time of her clot which demonstrated a 10-cm uterus and a 5.5-cm right ovarian cyst. The study was performed because she presented with a right-sided clot that extended from the calf through the thigh and into the pelvis.

Nineteen of the 30 participants (63%) with a DVT on tamoxifen had a predisposing event.

5. Overall, tamoxifen increased the risk of DVT compared to placebo. If the two subclavian clots are removed from the placebo group (related to extrinsic compression and a foreign body) and the clot that occurred on open-label tamoxifen is attributed to the tamoxifen arm, the numbers are 16 on placebo and 31 on tamoxifen. There is almost a doubling of risk with tamoxifen, even though women on placebo were more likely to have a predisposing factor for DVT.

6. The NSABP presented DVT by age of randomization (Table 59). The following table summarizes age at the time of event with annual hazard rates. Joseph Costantino, Ph.D., NSABP statistician, ran this analysis at our request:

Table 62. Age at the time of DVT with annual hazard rates

Event	Number of Events		Rate/1000 Women		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
DVT:	19	30	0.79	1.26	1.59	0.86-2.98
≤ 49	6	9	0.64	0.97	1.52	0.48-5.19
≥ 50	13	21	0.89	1.44	1.62	0.77-3.51

When age at event is examined, women over age 50 had a greater increase in the absolute number of events than did women under the age of 50. However, both women under 50 and women over age 50 experienced a 50% increase in the number of events. None of the increases, whether measured in the total population, by age at randomization, or by age at event, was statistically significant.

If one looks only at women with DVT on study drug or within 1 month of stopping study drug by age:

Table 63. Age at the time of DVT while on study drug or within 1 month of stopping study drug

Age at DVT	Placebo	Tamoxifen	Increase
≤ 49	3	9	3-fold
≥ 50	5	21	4-fold

This analysis supports the following observations:

- Clots are more commonly seen in postmenopausal women but still occur at a significant frequency in premenopausal women; the relative risk is the same although the absolute risk is greater in the postmenopausal setting
- Premenopausal women may become postmenopausal during the period of tamoxifen therapy, and this issue should be included in a risk-benefit discussion with a potential participant

7. An additional concern that emerged during review of the CRFs was the delay in diagnosis of deep vein thromboses. The tamoxifen prevention study was well-publicized with open discussion of potential adverse events in both the medical literature and in the lay press. Participants were required to sign a multi-page consent form that clearly outlined potential risks, including the risks of thrombotic events. However, one woman with a DVT on the placebo arm (5%) and seven women with DVTs on the tamoxifen arm (23%) had delays in diagnosis ranging up to 4 weeks that can be attributed to their physicians, not to participant non-compliance or participant's failure to seek medical care. With one exception, it was not possible to determine from the CRFs whether women informed the treating physician that they were on the NSABP P-1 study. The woman on placebo and 5 of the 7 women on tamoxifen had clot in the thigh, with an increased risk of pulmonary embolus. These cases are detailed below:

Placebo:

P53043TOL Participant presented to the ER with leg pain after a fall. The ER physician felt her exam was unremarkable and performed a diagnostic study at the insistence of the participant. The study was positive for deep vein thrombosis. Site: thigh.

Tamoxifen:

P24253CON Participant had a history of lower extremity calf pain. Was seen by an orthopedist and a neurosurgeon with negative examinations and was given the diagnosis of a slipped disc. The diagnosis of a DVT was made 4 weeks after initial evaluation when the participant presented to the ER with increasing swelling, warmth, and pain. Site: calf

P47476HOP Called physician on call with complaints of pain and swelling in the calf and behind the knee. Was advised to elevate the leg and take non-steroidal anti-inflammatory drug and to go to the ER if the pain increased. The participant sought medical attention within a few hours and was found to have a DVT. Site (thigh versus calf) not reported.

P36141MAR Called physician with leg pain; was told to elevate leg. She called back with increasing pain and was told to go to the ER, where a diagnosis of DVT was made. Site: thigh

P12185PGH Called with 3-day history of leg swelling and pain. Was told to elevate leg and apply heat TID before undergoing diagnostic evaluation. Time interval between phone call and diagnosis not stated in the CRF. Site: thigh

P16286STA Participant was seen by the PI of the BCPT at that site with complaints of unilateral lower extremity swelling. As documented in the record, the coordinator "encouraged a work-up with her local physician." The records indicate that this visit date was the last date of study drug administration. The participant was not seen by her local physician until 3 weeks later, when she was found to have a clot extending to the popliteal vein.

P30220PGH Participant was advised over the phone by the physician on call to take non-steroidal anti-inflammatory drugs for complaints of redness, swelling, and pain in the leg. Six days later she was diagnosed with a DVT in the femoral vein. Site: thigh

P08222MAR Participant was diagnosed with SCCA of the vulva and on the same day was given the diagnosis of superficial thrombophlebitis. Twelve days later, on her preoperative evaluation prior to radical vulvectomy, she was diagnosed with an extensive LE clot that extended from the calf into the thigh. Site: thigh

These cases underscore the need for careful monitoring during tamoxifen therapy. Women and their physicians should recognize the increased risk of thrombosis and should be prepared to have a low threshold for implementation of a diagnostic work-up. Women should be instructed to inform any treating physician that they are on tamoxifen. A Patient Package Insert will be helpful in underscoring this point.

7. Six protocol violations were noted, one on the placebo arm and 5 on the tamoxifen arm. These participants remained on study drug for one to seven months after the diagnosis of a DVT. One PI signed a note acknowledging the DVT and stating that the participant was given additional study medication. The majority of these violations, however, were because the BCPT treatment center was unaware that the participant had experienced an event until the next scheduled visit. Details can be found in section 8.5.3, Protocol violations.

Reviewer Comments: Pulmonary Embolus

1. In the course of reviewing CRFs for death, the reviewer found another pulmonary embolus in a patient on tamoxifen which resulted in her death.

P51364KEN This participant was a 65 year old woman at study entry whose other risk factors included a first degree relative with breast cancer. She had a biopsy-proven diagnosis of idiopathic pulmonary fibrosis made in 1994, prior to study entry. She began study drug on 9/6/96. On 3/4/97, study drug was discontinued because of increasing respiratory difficulties. She was placed on Imuran for the pulmonary fibrosis. She was admitted to the hospital 4/15/97 because of increasing shortness of breath, increased cough, and a history of a fever which resolved, and anemia with neutropenia attributed to the Imuran. She improved with antibiotics and transfusions, recovered her counts fully, and was afebrile off all antibiotics for 4 days. She then became acutely febrile and tachypneic with a sudden requirement for 50% oxygen supplementation. On 5/5/97, she was found cold and pulseless; resuscitation measures did not succeed. The provisional autopsy results indicated pulmonary fibrosis, possible right pulmonary artery thrombosis pending microscopic examination, mediastinal adenopathy with anthracosis, and LVH. The NSABP review coded her death as "idiopathic pulmonary fibrosis."

The reviewer was concerned that the participant had instead experienced a pulmonary embolus which, superimposed on her reduced pulmonary function, resulted in her death. We requested the final autopsy report from the sponsor, which was sent July 17, 1998. The final autopsy report noted a right pulmonary artery thromboembolus, with organizing microthrombi in smaller vessels. In addition, there was evidence of a transmural acute myocardial infarction, estimated to be between 3 and 10 days old. A small collection of malignant cells was found in one section taken from the right middle lobe.

The sponsor agreed with the reviewer that the participant experienced a fatal pulmonary embolus. There were therefore a total of 18 pulmonary emboli on the tamoxifen arm, 3 of them fatal.

2. Ninety-six percent of the pulmonary emboli were diagnosed in women aged 50 or more: 5 of the 6 PE in the placebo group and 18 of 18 diagnosed on tamoxifen.

3. Of the PE reported on the trial, all on the placebo arm occurred while the participants were on study drug. For the tamoxifen group, 6 PEs occurred 46 days to 29

months after discontinuing study drug. One of the events on the tamoxifen arm occurred in a participant who had been removed from study for a DVT. One occurred in the participant discussed in point 1, who was removed from study for a pulmonary event, but the pulmonary event was not identified as a PE until the autopsy.

4. Predisposing factors are summarized below.

Table 64. Predisposing factors for pulmonary emboli

Predisposing factor	Placebo	Tamoxifen
Surgical procedure	4	5
Comorbid condition	0	2*
Malignancy	0	3#
No predisposing events	2	8
Tobacco:		
Ever smoked	0	9
Currently smoke	0	3^
Weight:		
< 155 lbs	1	6
156-175 lbs	1	6
> 175 lbs	4	6

*CVA, pulmonary fibrosis leading to immobility

Pancreatic cancer; 2 breast cancers—one woman was receiving adjuvant chemotherapy at the time of the event

^ These women are included in the "Ever smoked" category

Women on tamoxifen with a PE were more likely to smoke (3/18) than women on placebo (0/6). Five of 6 women on placebo (83%) and 12/18 women on tamoxifen (67%) with PE were above the median weight in the trial.

5. It is reported in the medical literature that the incidence of pulmonary embolus is probably underreported for a variety of reasons. First, many physicians may not pursue the diagnosis of a PE in a patient with a documented DVT, as it adds expense and potential risk to a patient, if an angiogram is required, but does not change the management. Second, many pulmonary emboli are asymptomatic. Third, patients with PE may have significant comorbid illnesses that complicate or obviate additional work-up. The following cases were identified during the CRF review and may represent additional cases of "missed" PE.

Placebo:

P18988ALL The participant was 65 years old at study entry with a history of a first-degree relative with breast cancer. She began study drug 12/18/92 (randomized to placebo) and discontinued therapy 5/15/94 because of adverse publicity about the trial. She was diagnosed with a glioblastoma 11/26/96. A DVT of the thigh with extension through the calf vessels was diagnosed 12/3/96 and is included in the DVT listings supplied by the sponsor. A filter was inserted to prevent PE because of her CNS lesion

and contraindication to anticoagulation. On 12/7/96, she became acutely hypotensive and acidotic with prolonged PT and PTT levels and thrombocytopenia. The physician's note indicates that her cardiovascular parameters were not consistent with cardiogenic shock. She went on to develop renal and respiratory failure and expired. The cause of death was reported as glioblastoma multiforme.

P58494ARZ This 48 year old participant entered the trial with a history of one first-degree relative with breast cancer and 2 biopsies. She began study drug 9/21/92 and was randomized to placebo. A diagnosis of pancreatic cancer metastatic to the liver was made 2/24/97. On 4/26/97 she was found to have a DVT in the left superficial femoral, common femoral, and popliteal veins with extension into the iliac system. A V/Q scan was indeterminant: there were mismatched defects, but the perfusion defects were matched by radiographic abnormalities, such as pleural reaction and interstitial air space disease. She died 4/28/97 after rapidly progressive respiratory failure. Her death was attributed to pancreatic cancer.

Tamoxifen:
P58053WAY This participant was 47 years old with a history of 1 biopsy in the past, who began study drug 10/14/92 and was randomized to tamoxifen. She was diagnosed with a DVT 9/3/96 extending from the common iliac to the popliteal vein. She presented with right lower pleuritic chest pain and was found to have a pulse oximetry of 87%. Additional work-up for PE was not pursued.

P35134BOS A 59 year old participant with a first-degree relative with breast cancer was entered on the trial and randomized to tamoxifen. A brother also had breast cancer, but male relatives are not counted in the Gail model. She developed sharp left-sided pleuritic chest pain, but completed a scheduled cross-continental plane trip to California followed by a 5-hour car trip to her destination. She then developed calf swelling and presented for medical evaluation. A Doppler study showed a DVT in the left superficial femoral vein that extended through the popliteal vein. A V/Q scan showed patchy diffuse changes on both the ventilation and the perfusion scans. The radiologist felt the pattern was consistent with COPD. The chest X-ray demonstrated hyperinflation consistent with this interpretation. The participant had a 40 pack-year history of smoking and had quit 5 years prior to the event.

There may have been underreporting of PE in this trial, comparable to what occurs in clinical practice. However, the size of the study and the double-blind randomized design makes it unlikely that over-reporting occurred on one arm of the study and accounts for the difference in the incidence of thromboembolic events between the two arms.

6. Overall, tamoxifen increased the risk of pulmonary emboli and increased the risk of fatal pulmonary emboli. This event was limited, in the current study, to postmenopausal women. Smoking and obesity were associated with an increased risk, but did not account for all of the events.

Reviewer Comments: All thromboembolic events

1. The reported listings do not count multiple events in the same participant as separate events. Participants were always listed as the worst event, i.e., pulmonary embolus. These multiple events may be categorized as follows:

a. Recurrent DVT

On the placebo arm, four women experienced two or more clots. One of these women was the previously discussed participant with protein S/protein C deficiency.

No women randomized to tamoxifen experienced two or more DVTs without a PE.

b. Five participants, 3 on placebo and 2 on tamoxifen, presented with a simultaneous diagnosis of DVT and PE.

c. Two participants experienced DVT and PE, separated in time:

Tamoxifen:

P17129FXC This 50 year old woman (age at study entry) had a history of a first-degree relative with breast cancer and 1 biopsy. She began study drug 10/1/93 with tamoxifen and was diagnosed with breast cancer 8/11/95, causing her to be removed from study. She received 6 months of adjuvant CMF. She presented 1/19/96 with "pleurisy" and was felt to have pneumonia. A V/Q scan was obtained and was read as intermediate probability. She was treated conservatively. On 2/26/96 she was diagnosed with a DVT in the superficial femoral and popliteal veins. On 5/18/96, she presented with severe chest pain and a pO_2 of 68. A V/Q scan showed a segmental defect in the right mid-chest, called low probability for PE by the radiologist. The NSABP evaluated this finding and called the event a PE; she is reported among the PE events on study. The reviewer agrees with this assessment. She therefore experienced 2 documented events, DVT and PE, separated by 3 months. It is possible that the event of 1/19/96 was a PE, but there is no documentation to support this diagnosis.

P30001WOM This participant was 50 years old at study entry with a history of a first-degree relative with breast cancer and 1 biopsy for breast cancer. She began study drug 12/10/92 with tamoxifen. On 1/14/93, a clinical diagnosis of superficial phlebitis was made and she was treated with NSAID. On 2/9/93, a Doppler study showed a popliteal clot and a V/Q scan was read as high probability for PE. She was taken off study drug and treated with Coumadin until 12/22/93. On 1/6/94, a venogram demonstrated a new lower extremity clot. She required hospitalization and anticoagulation. The second DVT was not reported as a separate event in the database. Whether one considers the second DVT directly attributable to tamoxifen therapy or secondary to the initial clot, it should be considered as a long-term complication of the initial event.

2. Complications of a thrombotic event have not been discussed.

Among women reported to have DVT, no participant randomized to placebo experienced a long-term complication independent of second events. On the tamoxifen

arm, two women experienced chronic venous insufficiency that did not resolve during the period of observation in the study. One woman experienced a lower gastrointestinal bleed secondary to over-anticoagulation and required 5 units of PRBC and additional transfusions of fresh frozen plasma.

Among the participants with pulmonary emboli, one (P09227ILM), randomized to tamoxifen 6/24/93, was diagnosed simultaneously with a DVT and a PE 10/27/95 after presentation with pulmonary edema, right ventricular failure, hypotension, ventricular tachycardia, and renal insufficiency. The DVT involved the tibial, popliteal, and right superficial femoral veins. The PE was demonstrated by pulmonary angiogram to have blocked all flow to the right lung. She was treated with intra-arterial urokinase with restoration of blood flow to the lung followed by conventional anticoagulation. She was then found to have a large retroperitoneal bleed with a hemoglobin of 8.2 mg/dl. She required transfusions (number not given in the CRF). At the time of the bleed, the PT was 13.6 and the PTT was 68.3. A filter was placed.

3. Other thrombotic events

In section 10.5.2, Other Ophthalmologic Events, there are 2 safety reports of retinal vein occlusions that occurred in premenopausal healthy women without concomitant medical illnesses both randomized to tamoxifen. One occurred in a woman who had discontinued study drug 1 year previously; this event is unlikely to be related to tamoxifen administration. The other is temporally related and resulted in permanent vision deficit. There may be additional thrombotic complications of tamoxifen that have not been fully described or recognized in the course of the study. These events support increased risk in premenopausal women.

Reviewer Summary of Thromboembolic Disease:

1. Tamoxifen administration resulted in an increased risk of thromboembolic events. While the majority of events were seen in postmenopausal women, it appears that the relative increase in events for DVT was the same in both pre- and postmenopausal women, although the absolute difference was smaller for premenopausal women. Pulmonary emboli were predominantly seen in postmenopausal women. With the small number of PEs observed in the study, however, the reviewer does not feel that the risk of PE in premenopausal women can be discounted.

2. As with any thromboembolic event, a woman remains at increased risk for a second event, because of the underlying disorder that led to the first event (coagulopathies, obesity, tobacco use) in addition to anatomic abnormalities caused by the first event (altered venous architecture). Women considering tamoxifen for prevention of breast cancer should be apprised of the potential for complications of therapy-related and secondary events.

10.5 Ophthalmologic events

10.5.1 Cataracts

Evaluation of ophthalmic events on NSABP B-14 (tamoxifen versus placebo for estrogen receptor positive node negative breast cancer patients) suggested that tamoxifen administration might be associated with an increased incidence of cataracts. NSABP P-1 was designed to specifically examine this question in healthy women. Data regarding cataracts and cataract surgery, as described in the ERSMAC report, are presented in the following table.

Table 65. Relative risk of cataract surgery by baseline cataract status (Table 5, ERSMAC report, 1/31/98)

Cataract Status at Baseline	Participant status	Placebo	Tamoxifen	Rate Ratio	95% CI
Without cataracts at baseline	No. randomized	6230	6199		
	No. developed cataracts	483	540		
	Annual rate of cataracts/1000 participant-years	22.5	25.41	1.13	1.00-1.28
	No. cataract surgeries	63	101		
	Annual rate of surgery/1000 participant-years	31.43	46.62	1.48	1.08-2.03
With cataracts at baseline	No. randomized	477	482		
	No. cataract surgeries	66	100		
	Annual rate of surgery/1000 participant-years	46.20	72.89	1.58	1.16-2.15
Total	No. randomized	6707	6681		
	No. cataract surgeries	129	201		
	Annual rate of surgery/1000 participant-years	37.58	56.81	1.51	1.21-1.89

The manuscript submitted for the NSABP P-1 trial evaluated only randomized participants with follow-up:

Table 66. Average annual hazard rates of cataracts and cataract surgery among participants (Table 9, NSABP P-1 manuscript)

Event	Placebo	Tamoxifen	Rate/1000 Women		Risk Ratio	95% CI
			Placebo	Tamoxifen		
Without cataracts at randomization	6105	6073				
Developed cataracts	483	540	22.51	25.41	1.13	1.00-1.28
Developed cataracts and underwent cataract surgery	63	101	2.83	4.57	1.62	1.17-2.25

The authors noted that there was a 13% increased risk, of marginal statistical significance, of developing cataracts on tamoxifen treatment. Women who entered the trial with cataracts or who developed cataracts on study had a 62% increase in the need for cataract surgery.

Reviewer Comments:

1. Some women developed cataracts while followed on study, but after discontinuing study drug. Sixty-nine women on placebo and 99 women on tamoxifen had cataracts diagnosed 6 days to 5 years after stopping study drug. Fourteen and 16 participants respectively had cataract surgery 2 days to 3 years after stopping study drug.
2. Predisposing factors for cataract formation include age, diabetes mellitus, and some cholesterol-lowering drugs. A wide array of other etiologic factors is cited in the literature, but these factors were unlikely to occur in significant numbers of the study population. Tobacco use has also been questionably linked to cataract formation. These factors for the group of participants with cataracts at any time during the study are summarized below.

Table 67. Potential risk factors for women with cataracts at baseline or on study

Risk Factor	Placebo (n=960)	Tamoxifen (n=1022)	Total (n=1982)
Age:			
≤ 49	79	73	152
50-59	184	188	372
≥ 60	697	761	1458
Diabetes mellitus:			
No	887	941	1828
Yes	73	81	154
Past/current use of cholesterol-lowering medications:			
No	808	865	1673
Yes	152	157	309
Tobacco use:			
Ever smoked			
No	537	580	1117
Yes	423	442	865
Current smoker			
No	879	930	1809
Yes	81	92	173
Any one of the above (except age)			
No	428	456	884
Yes	532	566	1098

Age was the most common factor observed in women with cataracts. There were no imbalances between the treatment arms, and no factors other than age that appeared to predict cataract formation.

3. The incidence of cataract surgery by age was evaluated.

Table 68. Incidence of cataract surgery by age

Age	Placebo (n=129)	Tamoxifen (n=201)	Total (n=330)
≤ 49	6	8	14
50-59	18	28	46
≥ 60	105	165	270

Women over the age of 60 had the highest incidence of cataract surgery, as expected. Approximately half of the operations in each age group occurred in women with cataracts at study entry, and half in women who developed cataracts on study.

4. The cataract data suggest that tamoxifen may increase the incidence of cataracts. The 95% confidence interval for this calculation includes 1.00, and the observation is at the border of significance. These data also suggest that tamoxifen increases the risk of requiring cataract surgery. These observations imply that tamoxifen may accelerate cataract formation. Steroids have been associated with cataract formation; it is possible that the steroid characteristics of tamoxifen are responsible for this finding.

10.5.2 Other Ophthalmologic Events

The blank CRF contained a Report of Vision Abnormalities or Examinations form. This form reported the date of a vision exam and specifically asked about the development of cataracts, deterioration in previously-diagnosed cataracts, deterioration in the cornea, development of macular degeneration, or other problems, with space to specify the problem. Information on therapeutic interventions was also solicited. However, the NSABP stated in several meetings/teleconferences that only information on cataracts and cataract surgery was collected. At the request of the FDA, the NSABP submitted copies of safety reports made to the FDA on 7 individuals who experienced eye problems during the course of the study. These cases are described below:

Placebo:
P01618HOG This participant was randomized on 1/5/93 at age 52 to study drug (randomized to placebo). On 8/20/97, at age 57, she complained of black spots and wavy lines in the field of vision. She was diagnosed by her ophthalmologist with a retinal hole and underwent argon photocoagulation surgery to correct the problem.

P08935ARZ This 66 year old began study drug 12/23/92 and was diagnosed with glaucoma 8/94.

Tamoxifen:
P24757PGH This participant began study drug 5/7/93 with tamoxifen at age 44 and complained of blurred vision in the left eye 11/93. Study drug was stopped at this time because of problems with gastritis and mouth ulcers. On 1/10/95 she was diagnosed with a small branch vein occlusion.

P04291CIL This 47 year old participant began study drug 4/29/96 (randomized to tamoxifen). In 8/96, she noted cloudiness in her eye and vision loss, as well as bleeding in the left eye. On 8/24/96, her ophthalmologist diagnosed a non-ischemic venous occlusion. Study drug was discontinued 8/24/96. No therapy was instituted, and no improvement in her vision was noted. This participant was healthy, with no history of diabetes or hypertension, and was on no medications. Her PT, PTT, glucose, cholesterol, and platelet count were normal at the time of the event.

P49162MIA This participant began study drug 10/1/92 (randomized to tamoxifen) at age 60. On 7/25/96, at the age of 64, she was found to have macular degeneration of the left eye on routine examination. Study drug was discontinued.

P19123MID This participant began study drug in September 1992 (randomized to tamoxifen) at the age of 62. In October 1996, she noted difficulty reading. In December, cataract surgery with lens implant was performed. In February 1997, a macular hole in the left eye was diagnosed at the age of 67. Surgery was scheduled for 2/24/97. Study medication was discontinued 2/9/97.

P20701NVM This participant began study drug 10/17/93 (randomized to tamoxifen) at age 65. In June 1994, she was diagnosed with early cataracts and mild age-related macular degeneration. In December 1996, she saw an ophthalmologist for complaints of blurred vision (she was age 69). In the opinion of the ophthalmologist, the changes were age-related, not tamoxifen-related. She continued on study drug.

P14347ARZ This 68 year old participant was randomized 5/16/93 to study drug (tamoxifen). Because of complaints of decreased vision, she saw her ophthalmologist 5/19/97 at the age of 72 and was found to have early cataracts and age-related macular degeneration.

P39539HAW This 76 year old woman was randomized to tamoxifen and began study drug 5/11/93. Glaucoma was diagnosed 11/20/96, requiring trabeculectomy. She remained on therapy as of 12/11/97.

P35757MAN This 72 year old was randomized to tamoxifen and began study drug 9/18/92. Medication was discontinued 11/23/94 because of a diagnosis of glaucoma.

A database table of participants who reported a diagnosis of macular degeneration on study was provided 8/4/98. The database includes the participants listed above with macular degeneration.

Table 69. Macular degeneration in participants on NSABP P-1

Age	Placebo (n=65)	Tamoxifen (n=64)	Total (n=129)
≤ 49	12	4	16
50-59	13	10	23
≥ 60	40	50	90

Reviewer Comment:

1. Despite the structure of the form that included questions about a variety of ophthalmic complaints, not all of this information was incorporated into the database. In addition, participants were not required to have annual eye examinations.

2. The sponsor stated that cataracts and cataract surgery were the only eye findings noted during the trial. In the course of review of the CRFs, the following eye events were noted:

P47161TOL This 66 year old participant was diagnosed with macular degeneration 8/1/94, after starting study drug on 3/3/94. She went off-study at her request 10/30/95 because of her concerns about decreasing vision and worsening macular degeneration. She was randomized to tamoxifen.

P45660LBM This 56 year old participant was randomized to study drug with tamoxifen 3/14/94. She was noted on eye exam 2/3/95 to have corneal pitting. Study drug was stopped 11/5/95 because of a diagnosis of cancer of unknown primary.

The participant with macular degeneration was not listed in the database. If she is included, the number of women with macular degeneration on each arm of the study is equal.

3. The 7 MedWatch reports include 5 participants who have been reported in the database and in the above table for macular degeneration. The other 2 cases describe a venous occlusion of the eye, 1 that occurred on study drug and one that occurred after study drug discontinuation. These cases were discussed in Section 10.4.3, Thromboembolic events, and are likely to be related to the increased thrombogenesis associated with tamoxifen.

4. Review of available data does not demonstrate an increased risk of macular degeneration in participants on tamoxifen.

5. There is insufficient information to determine whether women are at increased risk of other, non-cataract- and non-macular degeneration-related eye events.

6. The consultation from the Division of Ophthalmologic Drug Products (Wiley A. Chambers, M.D.) noted the following:

- *The definition of cataract, the method of detection, the frequency of examination, type of cataract, and the reason for cataract extraction were not uniform throughout the study*
- *Despite these limitations, the finding of an increased rate of cataract extraction should not be ignored*
- *From review of the B-14 ophthalmologic substudy, clear differences in color vision testing and in the frequency of posterior subcapsular cataracts were observed. Posterior subcapsular cataracts are the most common drug-induced type of cataract.*
- *Recommendations for labeling were made*

10.6 Pregnancy

Women were required to indicate at several points during the pre-study evaluation that they were willing to use adequate contraception in order to enter the study. A warning about the risks to the fetus from tamoxifen was included in the consent form. Nonetheless, it is possible in a trial of this size and duration that pregnancies might occur.

At the FDA's request, the sponsor submitted information about pregnancies on study. This information is summarized below:

Table 70. Pregnancies during NSABP P-1

Patient Number	Treatment	Duration of Treatment; Pregnancy Outcome
P59068WAY	Placebo	Never started therapy; delivery Oct or Nov 1993
P28046PUG	Placebo	Started therapy 3/21/94 and continued until study unblinded. Pregnancy reported 5/95; miscarriage 5/26/95
P55959JSM	Placebo	Therapy started 5/25/94; continued until study unblinded. Positive home pregnancy test with request for unblinding; had elective abortion 8/28/95
P01016COL	Placebo	Therapy started 9/23/93; found to be 9 wks pregnant 1/24/94. Drug stopped until 2/17/94. Had miscarriage 2/12/94. Back on study drug until unblinding
P36420PUG	Tamoxifen	On study drug 11/13/92 to 12/17/92. Became pregnant 9/97. Pregnancy outcome unknown; more information pending

Reviewer Comment:

1. Overall, 5 women out of the 13,388 participants (0.04%) became pregnant, a sign of the highly motivated women in this trial.

2. During review of the CRFs, at least one participant (who did not become pregnant) was noted by a nurse to practice rhythm as a means of birth control (P52284EIN). Rhythm is not considered an effective means of birth control.

3. The sponsor sent information about P36420PUG. She delivered a healthy baby boy January 26, 1998. Postpartum exam was normal. No reported problems with the infant as of 5/28/98.

4. It will be important to include a detailed section in the label warning physicians and women about the potential risks of pregnancy with this drug. A Patient Package Insert will be helpful.

10.7 Adverse Events

10.7.1 Hematologic/Systemic adverse events

Adverse events were solicited from the Quality of Life forms, which included 42 symptoms. Participants filled out these forms, rating each event in severity from 0-4. Bloodwork was obtained at each visit, specifically WBC, platelet count, SGOT or SGPT, bilirubin, creatinine, and alkaline phosphatase. These results were then recorded on the

ADR form by the study coordinator at each site. The specific symptoms were placed in NCI CTC categories with grades at the local site. Forms were reviewed centrally.

Information is taken from the ERSMAC report that was presented March 24, 1998 and included patient data up to January 1, 1998 and from the database tables containing grade 3-4 adverse events from the ADR forms (sent 7/29/98), grade 3-4 gynecologic symptoms (sent 8/3/98), and grade 3-4 laboratory values (sent 7/31/98). Only participants with follow-up, not all randomized participants, were included in the analysis by the NSABP. The results are summarized in the following table. Neuro-mood scores are discussed in Section 11.0, Quality of Life.

Table 71. Grade 3-4 adverse events, NSABP P-1 trial

Adverse Event	Placebo	Tamoxifen	Total
WBC	3	1	4
Platelets	2	6	8
SGOT	1	0	1
SGPT	0	1	1
Bilirubin	0	3	3
Creatinine	9	7	16
Alkaline phosphatase	9	2	11
Cardiac dysrhythmia	15	10	25
Cardiac function	7	4	11
Hypertension	47	52	99
Hypotension	1	3	4
Neuro-sensory	6	5	11
Neuro-motor	8	9	17
Neuro-cortical	3	2	5
Neuro-cerebellar	1	2	3
Neuro-headache	19	29	48
Neuro-constipation	2	2	4
Neuro-hearing	1	3	4
Neuro-vision	9	17	26
Hemorrhage	1	1	2
Infection/sepsis	8	5	13
Nausea	8	6	14
Vomiting	6	3	9
Diarrhea	13	8	21
Stomatitis	0	2	2
Hematuria	2	1	3
Alopecia	3	4	7
Pulmonary	12	7	19
Skin	5	4	9
Allergy	9	9	18
Fever	2	1	3

Reviewer Comments:

1. The original submitted database did not allow an assessment of the number of women with elevated liver enzymes or hematologic abnormalities. Grade 3-4 ADR events and primary laboratory data were submitted 7/29, 7/31, and 8/3/98.

2. Hematologic parameters

There were no significant differences between WBC counts between the two groups. Few women had grade 3-4 platelet abnormalities. In the ERSMAC report, the number of women with platelet abnormalities of any grade was reported as 18 on placebo compared to 43 on tamoxifen. It is possible that tamoxifen is associated with thrombocytopenia; however, these data suggest that if there is an association, thrombocytopenia is a rare event.

No information on hemoglobin or hematocrit levels was collected.

2. Liver Function Test Abnormalities

In the database, as reported in Table 60, 1 participant on each arm had an elevation of either SGOT or SGPT. However, the ERSMAC report states that 9 participants on placebo and 7 on tamoxifen had grade 3-4 elevations of SGOT, and that 9 and 2 respectively had grade 3-4 elevations of SGPT. If an Access query is performed on the original toxicity database (BCPT2), 14 participants on placebo and 8 on tamoxifen experienced a grade 3-4 elevation of either SGOT or SGPT. Overall, there were more transaminase elevations on placebo than on tamoxifen.

Three patients on tamoxifen had grade 3-4 bilirubin elevations compared to none on placebo.

There were no differences in the incidence of rises in alkaline phosphatase; if anything, there were more elevations of any grade on placebo (97 v. 46).

3. The incidence of other adverse events was not significantly different between the two treatment arms. However, review of the case report forms indicated that events may have been missed. The database contains only information reported at scheduled visits. Adverse events are more likely to occur at timepoints that do not correspond to scheduled appointments.

10.7.2 Gynecologic Symptoms

There are no CTC grades for hot flashes or vaginal discharge, 2 well-recognized symptoms associated with tamoxifen. The following categories were therefore used:

Level 0:	No symptoms or symptoms were not bothersome
Level 1:	Slightly bothersome
Level 2:	Moderately bothersome
Level 3:	Bothered quite a bit
Level 4:	Extremely bothersome

Hot flashes and vaginal discharge were more common and more severe on the tamoxifen arm compared to control. These symptoms are shown in the following table:

Table 72. Gynecologic symptoms among NSABP P-1 participants (ERSMAC report, Table 1, page 32, volume 109.3)

Self-reported symptom/level	Placebo (n=6469)*		Tamoxifen (n=6441)*	
	No. Pts.	%	No. Pts	%
Hot flashes:				
Level 0	2053	31.7	1269	19.7
Level 1	1184	18.3	909	14.1
Level 2	1398	21.6	1352	21.0
Level 3	1189	18.4	1794	27.9
Level 4	645	10.0	1117	17.3
Vaginal discharge:				
Level 0	4230	65.4	2908	45.1
Level 1	1408	21.8	1686	26.2
Level 2	544	8.4	1058	16.4
Level 3	212	3.3	591	9.2
Level 4	75	1.2	198	3.1
Vaginal bleeding				
Level 0	5057	78.2	4974	77.2
Level 1	682	10.5	741	11.5
Level 2	399	6.2	387	6.0
Level 3	208	3.2	215	3.3
Level 4	123	1.9	124	1.9
Vaginal dryness				
Level 0	3140	48.5	3094	48.0
Level 1	1140	17.6	1135	17.6
Level 2	993	15.4	987	15.3
Level 3	694	10.7	769	11.9
Level 4	502	7.8	456	7.1

* Number of participants with follow-up QOL forms

Overall, hot flashes of any severity were reported in 68% of the placebo patients and in 80% of the tamoxifen patients. Level 3-4 hot flashes were reported in 28% of women on placebo and in 45% of women on tamoxifen. For vaginal discharge, the report of any severity occurred in 35% of women on placebo and in 55% of women on

tamoxifen. Level 3-4 events occurred in 4.5% and 12.3% of participants respectively. There was no difference in the incidence of vaginal dryness or vaginal bleeding between the two treatment arms.

11.0 Quality of Life analyses

The NSABP provided copies of the QOL analysis to the FDA on July 31, 1998. The introductory statement indicated that this analysis and slides had been prepared for a presentation at the Annual Meeting of the Society for Clinical Trials May 17-20, 1998.

In the analysis, data from 11,064 women randomized in the first 24 months of the study were used. The data was obtained at baseline and at follow-up at 3, 6, 12, 18, 24, and 36 months. This group of women was equally distributed by age group between tamoxifen and placebo, and the age distributions were similar to those of all 13, 388 participants in the BCPT trial. Three components of the Quality of Life questionnaire were analyzed: the Center for Epidemiological Studies--Depression Scale (CES-D), the Medical Outcomes Study (MOS), and the Sexual Activity Item from the MOS Sexual Functioning Scale.

The CES-D measures "non-specific psychological distress"--the items are related to affective distress but not to a particular psychiatric disorder. The data was presented as the mean score of all analyzed participants by treatment arm at each timepoint, and also stratified by the age groups 35-49, 50-59, and age 60 or older. A second series of tables showed the proportion of participants at each timepoint with a score $\geq$ 16, as 16 is considered the upper limit of normal, for the entire group and by age. All of these curves are superimposable and show no difference between treatment arms or differences between age groups. Each age group had approximately the same mean score, and no differences from baseline to the 36-month timepoint were observed.

The MOS analysis used the mean Physical Summary Scale and the mean Mental Health Summary Scale. These scales permit comparison with the general population of the United States as well as between-scale comparisons. The mean in the U.S. general population is defined as 50. The scales show no difference between treatment arms for the entire group or the subsets by age; there does not appear to be any difference in mean scores between the age groups. The scales appear to fall along a mean of 50, consistent with the mean in the general population. There was no difference between baseline and 36 month scores.

The Sexual Activity Item reports on the proportion of BCPT participants who were sexually active during the 6 months prior to each evaluation. Approximately 60-65% of the entire BCPT population was sexually active during the trial. The proportion of participants who were sexually active varied according to age:80% of women aged 35-49 were sexually active, compared to 65-70% of women aged 50-59 and 40% of women over the age of 60. There was no difference between treatment arms overall or by age; the proportions did not vary significantly over the 36-month time period that was studied.

Reviewer Comment:

1. There was a two-month delay in submitting the analyses, despite our agreement to accept the final analysis only rather than the raw data.

2. As described in the next comments, the CES-D scores were submitted. The statistical reviewer, Tony Koutsoukos, Ph.D., evaluated all randomized participants for extent of missing data. There is a gradual decline in the amount of missing data until approximately 36-42 months; after this timepoint, there is an acceleration in the amount of missing data, consistent with the unblinding of the trial. For the subset of women used in the QOL analyses, the pattern and amount of missing data appears to be the same between the two treatment arms.

2. Because of reports in the literature that associated tamoxifen with depression and because of the higher grades of depression reported during the trial, the Division chose to examine this aspect of the Quality of Life assessment in greater detail. At the request of the FDA medical reviewer, the QOL form with the CES-D and the depression scores for each participant were submitted.

The QOL questionnaire consisted of an 8-page form; the second page of the questionnaire contained the CES-D scale, which is comprised of 20 statements. The statements were a list of feelings, attitudes, and behaviors ("I was bothered by things that usually don't bother me"). Participants were asked to describe how often they had experienced these feelings in the past week: rarely or none of the time (less than one day), some of the time (1-2 days), moderately (3-4 days), or most of the time (5-7 days). These responses were scored from 0 to 3. A score of 15 or less is considered normal.

3. We first looked at the prior history of depression, nervous or emotional disorder, or psychiatric problems in the study population, and past or current use of antidepressants or tranquilizers.

Table 73. Past history of depressive/psychiatric illness and past/current use of antidepressant medication

Condition	Placebo (n=6707)	Tamoxifen (n=6681)	Total (n=13,388)
PHx depression, nervous/emotional disorder, psychiatric problem			
No	5535	5471	11,006
Yes	1172	1210	2382
Currently on antidepressants or tranquilizers:			
No	6020	5974	11,994
Yes	687	707	1394
Previously on antidepressants or tranquilizers			
No	4829	4792	9621
Yes	1878	1889	3767
Any past or present use of these drugs			
No	4794	4755	9549
Yes	1913	1926	3839

Only about 64% of the women on each arm with a past history of antidepressant or tranquilizer use stated that they had a prior history of depression, a nervous/emotional disorder, or psychiatric problems. Antidepressants are used for a variety of non-psychiatric conditions, but the medical reviewers noted, in reviewing the requested CRFs, that participants often added a note identifying a psychological reason for the use of the medication. Some participants may not have viewed short-term use of these medications in the past as consistent with a psychiatric diagnosis.

4. Review of the case report forms indicates that the baseline depression scores were assessed prior to randomization and were forwarded to the NSABP Biostatistical center. On the results of the entry/eligibility review, a "special note" was included if a woman's score exceeded the normal cut-off. However, there is no indication that P.I.s were required to discuss this finding with participants or perform further evaluation/treatment.

5. Information about depression was gathered in two ways: by a "Neuro-mood" toxicity grading obtained through the patient's self-reported symptoms and discussion with the study coordinator, and by the depression scores, calculated from the CES-D. The following table reports the distribution of neuro-mood toxicity in the trial:

Table 74. (Table 2, ERSMAC report, volume 3, page 12). Distribution of participants by depression grade.

	PLACEBO (N=6484)		TAMOXIFEN (N=6492)	
Depression Grade	No. pts	%	No. pts	%
None (0)	5785	89.2	5740	88.4
Mild (1)	317	4.9	313	4.8
Moderate (2)	328	5.1	375	5.8
Severe (3)	33	0.5	36	0.6
Suicidal (4)	20	0.3	26	0.4
Death (5)	1	<0.1	2	< 0.1

These figures were verified by the reviewer in an MS Access query of the database.

The tamoxifen arm had a greater number of participants with grade 3-5 depression: 64 compared to 54. In 2 patients treated with tamoxifen and 1 patient treated with placebo, the depression led to suicide. Overall, the NSABP felt there was a slight shift towards higher grades of depressive toxicity associated with tamoxifen, as stated in the ERSMAC report.

6. Based on this concern, the NSABP evaluated the depression scores for the women in the study:

Table 75. Distribution of highest depression score reported by NSABP P-1 participants (ERSMAC report, Table 3, page 13, volume 109.3)

	PLACEBO (N=6469)		**TAMOXIFEN (N=6441)**	
Depression Scores	No. pts	%	No. pts	%
0-15	4261	65.9	4242	65.9
16-22	1032	16.0	998	15.5
23-29	610	9.4	642	10.0
30-36	334	5.2	325	5.0
37+	232	3.6	234	3.6

Because there was no difference in the range of scores reported, the NSABP concluded there was no difference in the incidence of depression between the two arms.

7. We examined the range of depression scores in participants who had reported grade 3 through grade 5 neuro-mood toxicity.

Table 76. Range of depression scores for participants with grade 3, 4, or 5 neuro-mood toxicity

Grade, Neuro-mood toxicity	Placebo	Tamoxifen	Total
Grade 3:	33	36	69
Depression scores			
0-15	9	9	18
16-22	6	2	8
23-29	5	9	14
30-36	6	5	11
≥ 37	6	11	17
Unknown	1	0	1
Grade 4:	20	26	46
0-15	1	3	4
16-22	5	3	8
23-29	2	3	5
30-36	4	1	5
≥ 37	8	15	23
Unknown	0	1	1
Grade 5:	1	2	3
0-15	0	0	0
16-22	0	1	1
23-29	0	0	0
30-36	1	1	2
≥ 37	0	0	0

These data show that even within severe grades of reported neuro-mood toxicity, a wide range of depression scores was reported. The 2 measures did not always correlate.

8. In order to assess why these measures did not correlate, we examined data from participants identified in the requested CRFs. When the reviewers looked at the CRFs for other endpoints, we noted whenever a participant reported "feeling depressed" and also collected information on the initiation of antidepressant drugs. We did not include antidepressant drugs started for non-psychiatric reasons. [For example, some participants used these medications for fibromyalgia.] We then looked at the depression scores recorded around the time of the event.

Placebo:

P53043TOL Randomized 10/8/93; stopped drug therapy 4/18/94
Began Paxil 1/97
No scores obtained after 10/94

P34728DEN Randomized 7/23/92; stopped drug 7/25/94
Reported depression from the 3/31/94-7/25/94 follow-up
Depression score 7/24/94 14

P51290ELF Randomized 10/21/92; stopped drug therapy 11/7/94
12/9/96: "profound depression requiring medical therapy"
No scores obtained after 10/19/94

P02264BCC Randomized 10/26/92; off study 4/1/96
5/3/95: begun on antidepressant medication
Depression scores: 4/24/95 16
10/25/95 5

P54708DUL Randomized 10/15/92; off study approximately 10/24/97
Began Prozac while on study
Baseline depression score = 6
All others taken on study range from 25 to 43

P11454USA Began study drug 3/15/94; stopped drug 8/12/94
6/9/94 Recorded with depression
Depression scores: 1/28/94 11
6/9/94 15

P45196JSM On study drug 9/23/92; remained on drug as of 9/17/97
Antidepressant medication started 3/95
Depression scores: 9/21/94 37
3/28/95 37
9/19/95 22

P01130HOG On study 1/26/94; remained on study drug as of 2/3/98
Zoloft prescribed 1997
Trazodone prescribed 8/87
Depression scores: 1/31/97 52
7/31/97 45

Tamoxifen:

P08222MAR Randomized 9/15/92; stopped drug therapy 12/26/92
Began Prozac 9/94
Last depression score obtained 5/16/94 = 7

P15990NVM Randomized 3/17/93; stopped drug 11/1/94
Begun on antidepressant drug therapy 4/94
Depression scores: 10/6/93 0
6/1/94 11

P06358GRE Randomized 1/4/93; drug stopped 7/7/96
11/30/94 Amitryptilene begun
Depression score: 7/1/94 23
1/4/95 11

P09227ILM Randomized 6/10/93; drug stopped 10/26/95
6/15/95 Depression requiring medical therapy
Depression scores: 12/12/94 16
6/15/95 5

P02137BAY	Randomized 9/2/92; off study approximately 7/96		
	3/93 Reported as "severe depression"		
	Depression scores:	11/30/92	9
		3/3/93	7
		9/8/93	3
P19647 CON	Randomized 12/3/92; off study 7/29/93		
	Reported mild depression in the follow-up period 6/13/93 to 12/29/93		
	Depression scores:	3/10/93	5
		6/11/93	5
		3/18/94	2
P09500STA	Began study drug 5/19/93; stopped drug 19/9/96		
	3/6/96 Elavil prescribed for depression		
	Depression scores:	6/28/95	8
		3/5/96	12
P52758OCH	Began study drug 8/24/92; off drug 2/7/95		
	Described with depression in the follow-up period 8/26/93-2/28/94		
	Depression scores:	2/25/93	3
		8/24/93	8
		2/27/94	14
P18057HOG	Began study drug 2/10/94; off study 3/31/97		
	Began Zoloft 7/11/94		
	Depression scores:	5/9/94	7
		9/9/94	1
P21322MSU	Began study drug 8/9/92; stopped drug 1/10/97		
	Prozac started in 1995		
	Depression scores:	8/2/94	18
		2/15/95	29
		1/31/96	22
P12855SCR	Began study drug 9/3/92; off therapy 7/2/97		
	Prozac begun 1994		
	Zoloft begun 1996		
	Depression scores:	3/2/94	12
		9/16/94	17
		3/6/95	15
		10/6/95	18
		3/14/96	11
		12/2/96	15

The women who committed suicide on study are described separately below:

Placebo:

P09252BAS Randomized 12/10/93; stopped study drug 1/14/95
Died from suicide 11/4/95

Depression scores:	11/23/93	3
	4/12/94	1
	7/3/94	41
	1/5/95	42
	7/14/95	18

Tamoxifen:

P03512PUG Randomized 11/18/92; off study 11/24/97 because of death from suicide
Suicide attempt 5/4/94

Depression scores:	11/3/93	6
	5/17/94	48
	11/17/94	1

Suicide attempt 9/5/97

Depression score	5/19/97	3

Suicide 11/24/97

Depression score	11/10/97	49

P19608TOL Began study drug 9/4/92; off study 4/8/96 due to suicide
1/7/94 Prozac prescribed

Depression scores:	9/1/93	5
	3/9/94	14

4/8/96 Suicide

Depression score	2/26/96	5

No additional values

The data from women who did not commit suicide show that out the 19 women discussed, 11 had normal depression scores or had not had depression scores obtained around the time of the event. Of the 8 remaining women, 3 had grade 1 scores, 2 had grade 2, and 3 had grade 4 scores. In the women who committed suicide, scores were high around the time of a reported suicide attempt, but were normal at other points.

An additional 4 participants were identified, all randomized to tamoxifen, who did not have depression scores reported in the database table. Three decided to go off study because of depression (P32626NVM, P38084TOM); one went off study and reported depression requiring medication within 1 month of stopping study drug.

This information suggests several points:

- Depression scores are likely to be accurate only if taken at the time of the participant's acute distress
- A number of the participants began drug therapy when scores were grade 0-2. One possibility is that depression scores were not measured at the time of greatest distress; another is that clinical decisions are made on the basis of symptoms that score as